# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
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Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>07 July 1999 (07.07.99) | |
| **International application No.**<br>PCT/SE98/01717 | **Applicant's or agent's file reference**<br>2988615 |
| **International filing date** (day/month/year)<br>24 September 1998 (24.09.98) | **Priority date** (day/month/year)<br>23 October 1997 (23.10.97) |
| **Applicant**<br>LAAKSO, Timo et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 May 1999 (06.05.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|---|
| **The International Bureau of WIPO**<br>**34, chemin des Colombettes**<br>**1211 Geneva 20, Switzerland** | Authorized officer<br>F. Baechler |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01717

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/14, A61K 9/50, B01J 13/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAPLUS, EMBASE, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 4384975 A (JONES W. FONG), 24 May 1983 (24.05.83), column 3, line 18 - column 6, line 9 -- | 1-22 |
| A | US 4652441 A (CHIROAKI OKADA ET AL), 24 March 1987 (24.03.87), claims -- | 1-22 |
| A | US 5407609 A (THOMAS R. TICE ET AL), 18 April 1995 (18.04.95), column 3, line 49 - column 7, line 27 -- | 1-22 |
| A | US 4568559 A (ELIE S. NUWAYSER ET AL), 4 February 1986 (04.02.86), claims -- | 1-22 |

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 12 February 1999 | 22 -02- 1999 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Anneli Jönsson<br>Telephone No. +46 8 782 25 00 |

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internal application No.
PCT/SE 98/01717

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | EP 0052510 A2 (SYNTEX INC.), 26 May 1982 (26.05.82) -- | 1-22 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/02/99

Internal application No.
PCT/SE 98/01717

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 4384975 A | 24/05/83 | CH 648217 A,B | 15/03/85 |
| | | DE 3121983 A | 04/02/82 |
| | | FR 2484281 A,B | 18/12/81 |
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| US 4568559 A | 04/02/86 | US 4623588 A | 18/11/86 |

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/02/99

International application No.
PCT/SE 98/01717

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0052510 A2 | 26/05/82 | SE 0052510 T3 | |
| | | AT 21624 T | 15/09/86 |
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# PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference 2988615 | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/SE98/01717 | International filing date *(day/month/year)* 24.09.1998 | Priority date *(day/month/year)* 23.10.1997 |
| International Patent Classification (IPC) or national classification and IPC7 A 61 K 9/14, A 61 K 9/50, B 01 J 13/00 | | |
| Applicant BIOGLAN THERAPEUTICS AB et al | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 06.05.1999 | 09.12.1999 |
| Name and mailing address of the IPEA/SE<br>Patent- och registreringsverket<br>Box 5055<br>S-102 42 STOCKHOLM<br>Facsimile No. 08-667 72 88<br>Telex 17978 PATOREG-S | Authorized officer<br>Anneli Jönsson/Els<br>Telephone No. 08-782 25 00 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE98/01717

## I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☒ the international application as originally filed.

☐ the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☐ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☐ the drawings, ~~sheets~~/fig _____, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____,
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.
PCT/SE98/01717

**V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-22 | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | 1-22 | YES |
| | Claims | | NO |
| Industrial applicability (IA) | Claims | 1-22 | YES |
| | Claims | | NO |

2. Citations and explanations

The claimed invention relates to a method for encapsulating an active substance in a biodegradable polymer. The method comprises the steps of a) dissolving the biodegradable polymer in an organic solvent and b1) dispersing said active substance in the organic solution obtained in step a). A dispersion with the active substance as the inner phase thereof is provided, alternative to b1) involving the emulsifying of said active substance, dissolved in water or other aqueous solvent, in the organic solution obtained in step a). This provides an emulsion with the active substance as the inner aqueous phase thereof; c) subjecting the dispersion obtained in step b1) or the emulsion obtained in step b2) to an encapsulation operation with an aqueous polyethylene glycol solution as a continuous phase. Micro- or nanoparticles having the active substance encapsulated therein are obtained.

A method for preparing controlled or sustained release particles having a high entrapment of water-soluble substances is provided by this invention. Low energy mixing is also utilised. This is a convenient method for producing particles in micro or nano size. Previously used methods include the use of polyvinyl alcohol (PVA) and other surfactants. These undesired compounds are not necessary used in the claimed method.

US 4 384 975 A discloses how to form microspheres. The method is based on solvent removal from an oil-in-water emulsion. The initial removal of solvent causes the polymer to precipitate in a viscous liquid state and envelop the solid drug particles.

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**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Another document disclosing a method for solvent evaporation is US 4 652 441 A. This document discloses a water-in-oil composition comprising the active agent in the water phase and the polymer substance in the oil phase. Particles are formed after treatment and the solvent is desorbed from the oil phase. None of these documents disclose the claimed invention using polyethylene glycol as a continuous medium. Therefore, the documents cited above only disclose the general state of the prior art.

Document US 5 407 609 A discloses a method for microencapsulating an agent. The method comprises the steps of: a) dissolving or dispersing the active agent in a solvent, containing the wall-forming material, b) the dispersion from a) is combined with a continuous process medium, c) after formation of the emulsion in b), an extraction medium to extract the solvent is added. Microencapsulated product is formed. The document does not disclose the claimed invention's use of polyethylene glycol as a continuous medium. Therefore, the document only discloses the general state of the prior art.

Document US 4 568 559 discloses a method for preparing coated microparticles comprising medicaments. Particles comprising the active component are coated with a film-forming polymer in a fluidized bed. The polymer can be a polylactide, a polyglycolide or a copolymer of lactide and glycolide. However, the document does not disclose the claimed method or the use of polyethylene glycol as in the claimed method. Thus the document only discloses the general state of the prior art.
EP 52 510 A2 discloses the preparation of a pharmaceutical composition comprising a drug (such as a protein) and a polymer such as a poly (lactide-co-glycolide) copolymers. The method comprises dispersing an aqueous solution containing the polypeptide with a polymer hydrolysis-modifying agent in an organic solvent containing the encapsulating polymer. The formed particles are hardened, collected, washed and dried. The document does not disclose the claimed process. The document only discloses the general state of the prior art.

Consequently, the claimed invention according to claims 1-22 fulfils the requirements of novelty, inventive step and industrial applicability.

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference 2988615 | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/SE98/01717 | International filing date *(day/month/year)* 24.09.1998 | Priority date *(day/month/year)* 23.10.1997 |
| International Patent Classification (IPC) or national classification and IPC7 A 61 K 9/14, A 61 K 9/50, B 01 J 13/00 | | |
| Applicant BIOGLAN THERAPEUTICS AB et al | | |

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   - II ☐ Priority
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   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 06.05.1999 | 09.12.1999 |
| Name and mailing address of the IPEA/SE<br>Patent- och registreringsverket<br>Box 5055<br>S-102 42 STOCKHOLM<br>Telex 17978 PATOREG-S<br>Facsimile No. 08-667 72 88 | Authorized officer<br>Anneli Jönsson/Els<br>Telephone No. 08-782 25 00 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE98/01717

## I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☒ the international application as originally filed.

☐ the description, pages _____ , as originally filed,
pages _____ , filed with the demand,
pages _____ , filed with the letter of _____ ,
pages _____ , filed with the letter of _____ .

☐ the claims, Nos. _____ , as originally filed,
Nos. _____ , as amended under Article 19,
Nos. _____ , filed with the demand,
Nos. _____ , filed with the letter of _____ ,
Nos. _____ , filed with the letter of _____ .

☐ the drawings, ~~sheets~~/fig _____ , as originally filed,
~~sheets~~/fig _____ , filed with the demand
~~sheets~~/fig _____ , filed with the letter of _____ ,
~~sheets~~/fig _____ , filed with the letter of _____ .

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE98/01717

**V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-22 | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | 1-22 | YES |
| | Claims | | NO |
| Industrial applicability (IA) | Claims | 1-22 | YES |
| | Claims | | NO |

2. Citations and explanations

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A method for preparing controlled or sustained release particles having a high entrapment of water-soluble substances is provided by this invention. Low energy mixing is also utilised. This is a convenient method for producing particles in micro or nano size. Previously used methods include the use of polyvinyl alcohol (PVA) and other surfactants. These undesired compounds are not necessary used in the claimed method.

US 4 384 975 A discloses how to form microspheres. The method is based on solvent removal from an oil-in-water emulsion. The initial removal of solvent causes the polymer to precipitate in a viscous liquid state and envelop the solid drug particles.

.../...

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

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Document US 5 407 609 A discloses a method for microencapsulating an agent. The method comprises the steps of: a) dissolving or dispersing the active agent in a solvent, containing the wall-forming material, b) the dispersion from a) is combined with a continuous process medium, c) after formation of the emulsion in b), an extraction medium to extract the solvent is added. Microencapsulated product is formed. The document does not disclose the claimed invention's use of polyethylene glycol as a continuous medium. Therefore, the document only discloses the general state of the prior art.

Document US 4 568 559 discloses a method for preparing coated microparticles comprising medicaments. Particles comprising the active component are coated with a film-forming polymer in a fluidized bed. The polymer can be a polylactide, a polyglycolide or a copolymer of lactide and glycolide. However, the document does not disclose the claimed method or the use of polyethylene glycol as in the claimed method. Thus the document only discloses the general state of the prior art.
EP 52 510 A2 discloses the preparation of a pharmaceutical composition comprising a drug (such as a protein) and a polymer such as a poly (lactide-co-glycolide) copolymers. The method comprises dispersing an aqueous solution containing the polypeptide with a polymer hydrolysis-modifying agent in an organic solvent containing the encapsulating polymer. The formed particles are hardened, collected, washed and dried. The document does not disclose the claimed process. The document only discloses the general state of the prior art.

Consequently, the claimed invention according to claims 1-22 fulfils the requirements of novelty, inventive step and industrial applicability.

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D INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 9/14, 9/50, B01J 13/00

A1

(11) International Publication Number: WO 99/20253

(43) International Publication Date: 29 April 1999 (29.04.99)

(21) International Application Number: PCT/SE98/01717

(22) International Filing Date: 24 September 1998 (24.09.98)

(30) Priority Data:
9703874-9 23 October 1997 (23.10.97) SE

(71) Applicant *(for all designated States except US)*: BIOGLAN THERAPEUTICS AB [SE/SE]; P.O. Box 50310, S-202 13 Malmö (SE).

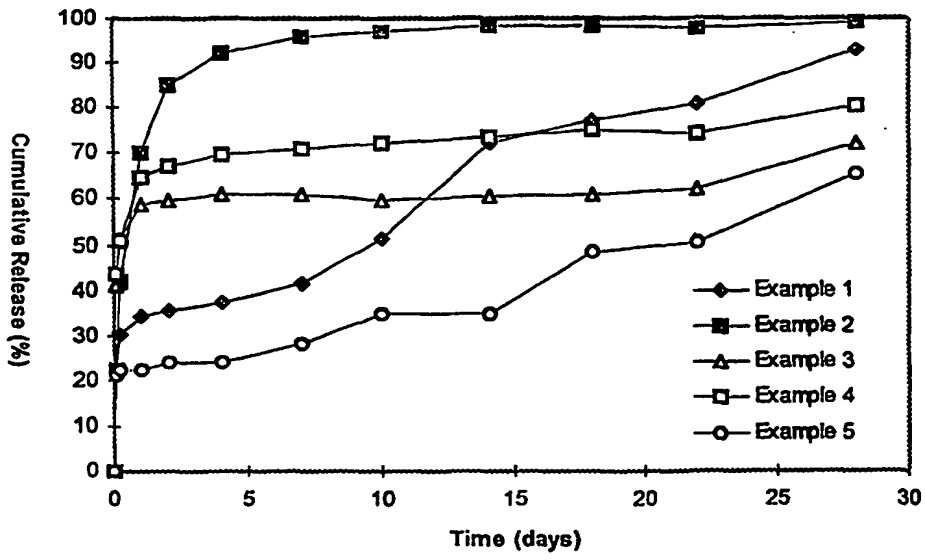
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LAAKSO, Timo [SE/SE]; Boltensternsväg 33D, S-236 38 Höllviken (SE). RESLOW, Mats [SE/SE]; Bondevägen 45, S-227 38 Lund (SE).

(74) Agent: AWAPATENT AB; P.O. Box 45086, S-104 30 Stockholm (SE).

(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: ENCAPSULATION METHOD




(57) Abstract

A novel method of encapsulating an active substance in a biodegradable polymer, which comprises: a) dissolving said biodegradable polymer in an organic solvent therefor; $b_1$) dispersing said active substance in the organic solution obtained in step a), to provide a dispersion with the active substance as the inner phase thereof; or alternatively $b_2$) emulsifying said active substance, dissolved in water or other aqueous solvent therefor, in the organic solution obtained in step a), to provide an emulsion with the active substance as the inner aqueous phase thereof; and c) subjecting the dispersion obtained in step $b_1$), or alternatively the emulsion obtained in step $b_2$), to an encapsulation operation with an aqueous polyethylene glycol solution as a continous phase, to provide micro- or nanoparticles having the active substance encapsulated therein. Sustained release particles obtainable therebs.

*FOR THE PURPOSES OF INFORMATION ONLY*

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| **CF** | Central African Republic | **JP** | Japan | **NE** | Niger | **VN** | Viet Nam |
| **CG** | Congo | **KE** | Kenya | **NL** | Netherlands | **YU** | Yugoslavia |
| **CH** | Switzerland | **KG** | Kyrgyzstan | **NO** | Norway | **ZW** | Zimbabwe |
| **CI** | Côte d'Ivoire | **KP** | Democratic People's Republic of Korea | **NZ** | New Zealand | | |
| **CM** | Cameroon | | | **PL** | Poland | | |
| **CN** | China | **KR** | Republic of Korea | **PT** | Portugal | | |
| **CU** | Cuba | **KZ** | Kazakstan | **RO** | Romania | | |
| **CZ** | Czech Republic | **LC** | Saint Lucia | **RU** | Russian Federation | | |
| **DE** | Germany | **LI** | Liechtenstein | **SD** | Sudan | | |
| **DK** | Denmark | **LK** | Sri Lanka | **SE** | Sweden | | |
| **EE** | Estonia | **LR** | Liberia | **SG** | Singapore | | |